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TRANSPORT BEHAVIOR AND RISK EVALUATION OF PHARMACEUTICAL CONTAMINANTS FROM SWASWA WASTEWATER STABILIZATION PONDS

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Abstract:
Researchers repeatedly discovered primary pharmaceutical contaminants, their metabolites, and transformation products in aquatic ecosystems. Although, body metabolism may not convert all consumed pharmaceuticals before excretion metabolic elements, clinical and industrial wastes ensure their presence in the environment. Nevertheless, conventional methods of wastewater treatments are ineffective for pharmaceutical wastes. Once in the ecosystem, they alter the physiological response of nontarget exposed aquatic and even terrestrial organisms due to induced toxicity. In the course of this study at Swaswa Wastewater Stabilization Ponds (SWSP), the transport of the quantified 0.104 ppm of metronidazole under advection mode in a laminar flow to a longitudinal predictive distance of 230 m. Beyond this distance, no significant concentration changes. The quantified metronidazole had a risk quotient of less than 1, implying no toxicity risks. Despite being acceptable, their hydrophobic nature and physiological activeness present a long-term ecological risk such as developing antibiotic resistance genes, endocrine disruption, and immunity suppression. A combination of engineered constructed wetlands and adsorption using biodegradable adsorbents are among natural remedial practices for eliminating pharmaceuticals with promising efficacy, cost-effectiveness and being environmentally friendly.

Keywords: Pharmaceutically active compounds, Pharmaceutical products, Risk quotient, Swaswa, Lipophilic efficiency

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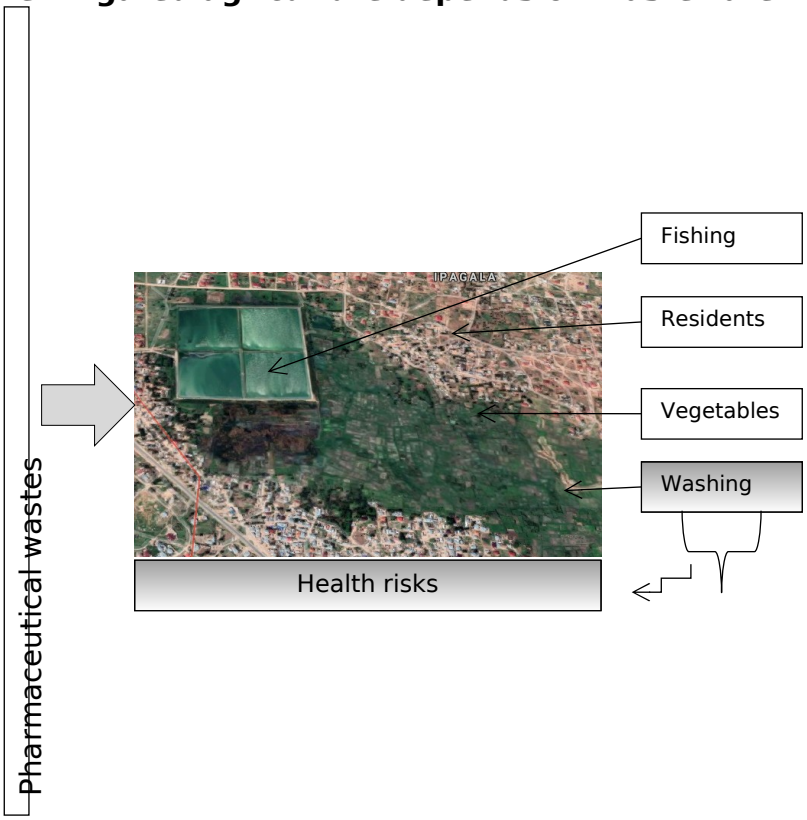
INTRODUCTION

Currently, social and economic development impose changes in lifestyle by adopting the use of industrially processed products such as canned foods and synthetic drugs for health care. Seeking modern shelters lead to increased urbanization that requires improved sanitation infrastructure. Human activities such as domestic, industrial, agricultural, wastewater treatment plants, reuse of sludge, hospital and municipal release contaminated wastewaters (Boberg et al., 2019; Finkel & Gray, 2021). In most developing countries, wastewater treatment uses waste stabilization ponds such as Swaswa in Dodoma city. However, the design of this method lack component for the removal of emerging contaminants (ECs), released effluents caries ECs such as pharmaceuticals to the environment (Badi et al., 2019; Marti et al., 2014). Drugs help treat humans, animals, and plants, prolong life, improve function, relieve symptoms, and alleviate pain (Choudhury & Veeraraghavan, 2018; Fragkaki et al., 2013; Han et al., 2017; Ratola et al., 2012). Pharmaceutically active compounds, metabolites, and transformation products in quantifiable levels of all drug categories reported exist in the environment worldwide, including Tanzania (Makokola, Sikudhani K. Ripanda, A. S. Miraji, 2020; Rastogi et al., 2015). Swaswa waste stabilization pond and the surrounding area where irrigated agriculture depends on wastewater are presented by Scheme 1.

Scheme 1. Swaswa waste stabilization pond and the surrounding area where irrigated agriculture depends on wastewater



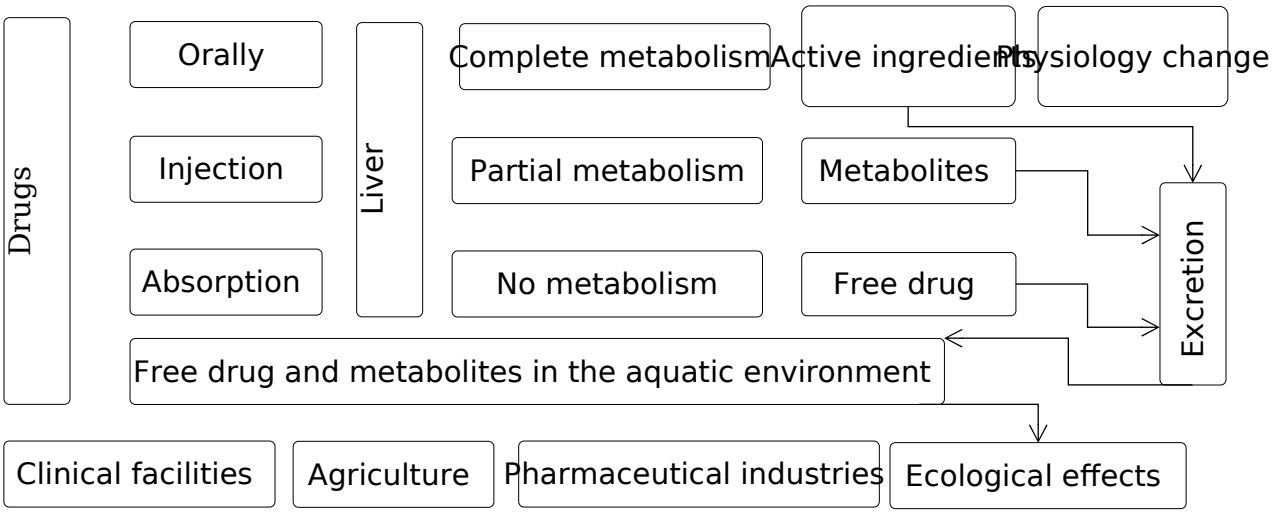
Report of about 90% of the antibiotics to be excreted via urine and feces when administered to humans and animals. Thus, a significant amount of antibiotics may pass through target organisms and then be deposited into aquatic systems (Felis et al., 2020; Hasan, 2018), hence the possibility of causing harm to the ecosystem. Pharmaceuticals are among the non-regulated chemical contaminants (Finkel & Gray, 2021; Jeong et al., 2020). These contaminants lack standard guidelines for their environmental monitoring and thus have drawn much scientific attention due to their health and presumed ecological risks (Li, Yan Zhang, Luyan Liu, Xianshu Ding, 2019; Munschy et al., 2020). Reports of endocrine disruption and antimicrobial resistance are concerns posed by contaminants of emerging concern such as pharmaceuticals (Teta et al., 2018). In an environmental aspect, antibiotics' most prominent effect is the toxic effect on aquatic organisms that may upset the ecological balance (Nantaba et al., 2020), leading to conservation failure.

Transport behavior of contaminants

Drugs for humans and animals come in various forms, including solids like metronidazole tablets (World Health Organization, 2013). The diverged physical states of these drugs enable choice for different roots of administering medication in the body, aiding high bioavailability and maximum drug efficacy (Jadhav et al., 2020; Yan Li et al., 2020; Schittny et al., 2020). Once a drug is in the body, Scheme 2 details the metabolic process it undergoes, basically being metabolized in the liver and its transportation to specific organs or excretion (Madikizela et al., 2017). Apart from body excretions, disposal of unused drugs is an essential root through which pharmaceuticals get in the environment, to which contaminated points become a point source (Richards et al., 2016, 2017). Several physical and chemical processes simultaneously occur on a chemical, mainly a pharmaceutical product, once exposed to the environment (Armstrong et al., 2018; Di Baccio et al., 2017; Ding et al., 2017; More et al., 2019; Poursat et al., 2019; Prasse et al., 2018). Natural processes affect

the physical distribution, containment, source-sink, degradation, bioavailability, bioaccumulation, and biomagnification of pollutants (A. Brown, 2019; A. K. Brown & Wong, 2018; Jadhav et al., 2020; Koller, 2018; Yuanbo Li et al., 2019; J. Lv et al., 2019; Ouda et al., 2021; Richmond et al., 2018; Rigg et al., 2018; Zhou et al., 2018). As a scheme result, they might affect the toxicity of a pharmaceutical product in an ecosystem. Induced factors affecting the transport of contaminants in flowing water include water withdrawing or pumping and secondary contaminant production (Awad et al., 2018; A. K. Brown & Wong, 2018; Gracia-Lor et al., 2020; Kołecka, Katarzyna Gajewska, Magdalena Stepnowski, Piotr Caban, 2019; Palacios-Rosas & Castro-Pastrana, n.d.; Soares et al., 2019). Inherently, analysts' decisions on the selection of computational values and limits such as Manning's constant (Oregon, 2014) and dimensionality of transport (Timis, 2010; Vinet & Zhedanov, 2011; Xiao Liu1, Takumi Ishizuka1, Hong-Liang Bao1, Kei Wada2, Yuuma Takada1, Keisuke lida3, Kazuo Nagasawa3, Danzhou Yang4, 1997; Yadav et al., 2010; Zeng & Huai, 2014) affect the mathematical output and, therefore, predictability of contaminant transport.

Scheme 2: Roots of pharmaceuticals to the body and environment
Pharmaceutical Risk Evaluation



Risk evaluation of pharmaceutical products is conducted with safety concerns to ensure that the benefits of these products to human, other organisms, and the environment outweighs their risks. Helping in better understanding, generating knowledge, and defining the regulatory and monitoring frameworks for the safety of the ecosystem (Cordaillat-Simmons et al., 2020). Gunnarsson et al. (2019) evaluated the environmental risk of more than 900 approved small molecule drugs targeting human proteins. About 90% lack a complete set of regulatory compliant ecotoxicity data in the public domain (Gunnarsson, Lina Snape, Jason R.Verbruggen, Bas Owen, Stewart F. Kristiansson et al., 2019). This study highlighted the requirement of a custom-made environmental risk assessment and a transparent database that captures and stores ecological data for various applications such as safety evaluation.

Nevertheless, greater than 80%) of drugs with a complete set of ecotoxicity data, risk quotients assuming worst-case exposure assessments were below one in all European countries, indicating low environmental risks for the endpoints assessed (Gunnarsson, Lina Snape, Jason R. Verbruggen, Bas Owen, Stewart F. Kristiansson, Erik Margiotta-Casaluci, Luigi Österlund, Tobias Hutchinson, Kathryn Leverett, Dean Marks, Becky Tyler, 2019). Developed countries have advanced treatment schemes

that incorporate the removal of pharmaceuticals, hence reducing ecological risk (Mir-Tutusaus & Sarrà, 2020). A lipophilicity assessment that describes the pharmaceutical partitioning coefficient in octanol-water is essential (Ali et al., 2018). It explains the ability of drugs to cross biological membranes such as brain barriers both in drug discovery (Lipinski et al., 2012) and in environmental toxicology (Ndunda, E.N., Wandiga, 2020). Therefore, the more lipophilic molecule may move more efficiently than less lipophilic (Williams, Hywel D. Ford, Leigh Han & Tangso, Kristian J. Lim, Shea Shackleford, David M. Vodak, David T. Benameur, Hassan Pouton, Colin W. Scammells, Peter J. Porter, 2018). The assessment of the ecosystem safety using lipophilic properties of the pharmaceutical drug to predict its fate in living organisms and propose the model of chemicals transport and accumulation in the ecosystem (Chmiel et al., 2019). The use of pharmaceuticals for human security is inevitable, thus creating a continuous deposition, transportation, and later human, animal, aquatic organisms and the entire ecosystem exposure. As a case, the current study focuses on understanding the transport behavior and risks upon exposure to pharmaceutical wastes from the Swaswa wastewater stabilization pond.

METHODS

Study area

Dodoma urban sits between 60° 00' and 60° 30' South and 35° 30' and 36° 02' East, covering an area of 2769 km^2 of which 542 km^2 is urbanized. Apart from population size, most people use on-site sanitation, while others use Swaswa WWSP located at Swaswa ward, 5 km from Dodoma city. Not everyone has access to sanitary sewers; instead, they must rely on private tankers. Duwasa provides home tap water and wastewater management (Makokola S.K; ASHA RIPANDA; Hosein MIRAJI, 2020). Dodoma has a long dry season from April to early December and a short single wet season that lasts for the remaining month. It has an average rainfall of 570 mm, and around 85 percent of this precipitation falls between December and April. Due to the dryness and modest population size, wastewater treatment is not a problem compared to the wet region of Tanzania, such as Dar es Salaam.

Sampling and Sample Collection

Wastewater effluents from Swaswa WWSP were collected in November 2017 to analyze pharmaceutical contaminants reported by Makokola *et al.* (Makokola S.K; ASHA RIPANDA; Hosein MIRAJI, 2020). Each 50 mL sample was stored in a pre-washed and three times rinsed umber glass bottle to avoid light that may induce an oxidation reaction. In addition, these samples were filtered to avoid analysis of pharmaceuticals adsorbed on the surface of suspended matters (Gilcreas, 1967). Although several studies have proposed using solid-phase extraction or solid-phase microextraction (D.A.Wells, 2000; Yang & Pawliszyn, 1994), this study adopted the air of extracting ECs via reverse phase liquid-liquid extraction technique (Xu et al., 2001) by using dichloromethane. The extracts were wholly dried and later reconstituted with polar solvent before analysis with Ultra Shimadzu QP 2010 GC/MS. Targeted pharmaceutical ECs were metronidazole, paracetamol, cetirizine, and ibuprofen. The float method [75] calculates water velocity using ice cubes, whereby the time taken to move ice cubes through a known distance is recorded and speed calculated. The obtained rate is multiplied by the surface area of the river floor to get the flow volume of that stream.

Data quality and consistency

All samples and measurements were taken in triplicate to ensure data quality with acceptable reproducibility. Method validation conducted through sample spiking resulted in 90 to 110 percent recovery, like the American Public Health Association (APHA) (Gilcreas, 1967).

Computation of contaminant transport

A mathematical overview of contaminant transport focuses on the initial or background concentration (Y. Lv et al., 2020) in the computation and prediction of

contaminant mobility and possible risk factors such as risked species and potential interventions. The advection movement of water in the direction of flowing water is given by Equation 1 (Jaiswal et al., 2011; Yadav et al., 2010).

$$T_{X_0}^{A} = u_{X_0} * A * C_{X_0} \quad \text{..... .1}$$

Advection is a passive transport due to movements of surface waters that account for the velocity of flowing water, the surface area of the river, and background concentration from a specified point source (Savina et al., 2010). Non-point sources with the either irregular or regular occurrence of a target contaminant are neglected in this case for simplicity (Anderson & Destouni, 2001). The dispersion transport Equation 2 accounts for diffusion and other factors affecting solutes' spreading, such as variations in the flow rate and longitudinal distance (Anderson & Destouni, 2001). Dispersion is a natural process resulting from the difference in the concentration gradient between the point of contamination against surrounding water.

$$T_{X_0}^{D} = -D_{X_0} * A * \left.\frac{\delta c}{\delta x}\right|_{X=X_0} \quad \text{..... 2}$$

Mobility of contaminants involves movements of a certain quantity of pollutants over a specific area of a river per unit time, which is a solute flux (Genuchten, 1981; Sander & Braddock, 2005). It is a process that involves both advection and dispersion processes, as indicated in Equation 3.

$$J_s = uC - D_x \frac{\delta C}{\delta x} \quad \text{.....3}$$

Where; u= fluid flow velocity (LT^{-1}), A= surface area (L^2), C= solute concentration (ML^{-3}), D_x= longitudinal dispersion coefficient ($L^{-2}T^{-1}$), x= longitudinal coordinate (L), M= mass. Because chemical contaminants enter and leave, mass conservation is inevitable (Pérez Guerrero et al., 2013; Yadav et al., 2010). Thus, a mass balance Equation 4 counts for the contaminant accumulation and degradation in which sink, sources, injection, and pumping processes that may affect the mass balance are taken care of as reported by other scholars (Y. Lv et al., 2020):

$$\frac{\delta C}{\delta t} = -\nabla * J_s - R_s - R_w C_e \quad \text{.....4}$$

Where; t= time (T), R_s= arbitrary sink [<0] or sources [>0] ($ML^{-3}T^{-1}$), C_e= concentration (ML^{-3}), R_w= injection [>0] or pumping [<0] of water ($L^3L^{-3}T^{-1}$), ∇= vector differential operator. Thus, combining Equation 3 and 4 give Equation 5.

$$-\nabla * J_s = \frac{\partial (J_s)}{\partial x} = D_x \frac{\delta^2 C}{\delta x^2} - u \frac{\delta C}{\delta x} \quad \text{.....5}$$

Other factors affecting transportation of contaminants include sediments density affecting sorption of contaminants, biodegradation, radioactive decay, and contaminant production are considered and taken care of by Equation 6 (Y. Lv et al., 2020; Yadav et al., 2010).

$$\frac{\delta C}{\delta t} = D_x \frac{\delta^2 C}{\delta x^2} - u \frac{\delta C}{\delta x} - \mu C + \gamma \quad \text{.....6}$$

Where; μ=general first-order decay rate (T^{-1}), γ=zero-order production term ($ML^{-3}T^{-1}$). The formulated equation six is the advection-dispersion equation (ADE) for the longitudinal transport of contaminants (Yadav et al., 2010). In the current study, the average velocity of water was 0.454 m/s, and the flow rate of 0.041 m^3/s. Among other conditions for a 1-D ADE, the most important ones are tabulated in Table 1.

Table 1: Advection-Dispersion Equation Transport Conditions

Conditions	Descriptions	Guiding equations	Referenc es

Initial boundary conditions	Concentration-distance relationship	$C(x,0)=f(x)$	
Diric condition	Contaminant of mass 'm' can be distributed over an infinitely small region	$f(x)=\frac{m}{A}\delta(x-x_o)$	
Infinite domains	Concentration-time factor	$\frac{\delta C}{\delta x}=(\pm\infty,t)=0$	(Zeng & Huai, 2014)
Dirachlet condition	Concentration is continuous across the interface at all times	$C(0,t)=g(t), t>0$	
Exit condition		$\left.\frac{\partial C}{\partial x}\right\|_{x=\infty}=g(t), t>0$	

Under the stated conditions in Table 2, Equation 6 can be numerically solved to give Equation 7. This equation is a 1-D equation relying on two variables, namely concentration and longitudinal distance (Pérez Guerrero et al., 2013).

$$c(x,0)=\frac{\gamma}{\mu}\left(C_b-\frac{\gamma}{\mu}\right)\exp\left(\frac{x(u-\varepsilon)}{4D_x}\right) \quad \text{..... 7}$$

Equation 7 is an exponential decay curve computed by using Matlab software. The dispersion coefficient Dx in Equation 8 is a fixed factor accounting for the physical properties, including average depth (H), speed of water as well as average width (B) of the river (Zeng & Huai, 2014).

$$D_x=5.4*\left(\frac{B}{H}\right)^{0.7}*\left(\frac{u}{U^*}\right)^{0.13}*Hu \quad \text{..... 8}$$

The moving water experiences friction on the rough surface of the river that retard the speed of moving water. The sheer velocity (U*) is presented in Equation 9, as similarly reported by (Zeng & Huai, 2014).

$$U^*=\frac{u}{h^{\frac{1}{6}}}8*n\sqrt{g} \quad \text{..... 9}$$

Contaminants decay is a natural process that might be triggered by natural forces such as heat, pressure, and weakening of forces holding atoms together (Zeng & Huai, 2014). As a result, concentration, transport behavior, and fate will be affected. In this case, the general first-order decay presented in Equation 10 accounts for the effects (Jaiswal et al., 2011).

$$\mu=0.18*\left(\frac{u}{U^*}\right)^{1.5} \quad \text{..... 10}$$

Psilon (ε), a velocity-based factor, integrates the decay effects, physical properties of river surface, and the overall mobility of contaminants. Equation 11 indicates how epsilon can be calculated (Yadav et al., 2010).

$$\varepsilon=u\sqrt{1+\frac{4\mu D_x}{u^2}} \quad \text{..... 11}$$

The obtained Equation 7 can be simplified to form a simple exponential decay curve with Equation 12 below.

$$c=P*\exp(Q*x) \quad \text{.....12}$$

$$P=\frac{\gamma}{\mu}\left(C_b-\frac{\gamma}{\mu}\right),\ Qx=\left(\frac{(u-\varepsilon)}{4D_x}\right)$$

Again the obtained Equation 12 can be linearized when a natural logarithm is applied. Yet, Equation 7 is computed by Matlab (Raei et al., 2017), resulting from an exponential decay function.

$$Risk\,quotient(RQ)=\frac{Measured\,concentration}{Reference\,Concentration}$$

The RQ value greater than 1 is likely to cause an effect upon exposure, while RQ less than 1 implies no possible harm expected to occur upon exposure. The reference concentration is the chemical concentration that causes toxicity to an organism for the specified exposure time. In this study, the reference concentration for metronidazole in freshwater fish was taken to be 100 mg/L/96 as reported in the ThermoFisher safety data sheet (Scientific, 2012).

RESULT AND DISCUSSION

This study investigated the presence of pharmaceuticals in wastewater from Swaswa waste stabilization ponds. Only metronidazole was present at a quantifiable level among the investigated drugs, while paracetamol, cetirizine, and ibuprofen were unavailable or below the detection limit. Medications are among the contaminants of emerging concerns characterized by mobility in the form of surface adsorption, free drug or metabolite, persistent due to their non-biodegradable nature (Grenni et al., 2019; Olowoyo & Mugivhisa, 2019) as well as resistance to on-site conventional wastewater treatment schemes leading to post-discharge environmental processes (Furlong et al., 2017). Special attention inevitably becomes obligatory.

Quantified pharmaceutical contaminants and their implications

These pharmaceuticals may potentially reach surface and groundwaters, essential drinking-water sources, and pose known and presented to harm the ecosystem (Khan et al., 2020; Vasquez et al., 2014). A joint study by the U.S. Geological Survey-U.S. Environmental Protection Agency examined source and treated waters from 25 drinking-water treatment plants across the United States. Results indicated the presence of pharmaceuticals in all source-water samples and quantifiable pharmaceutical detections were fewer, with a maximum of five drugs in any one sample and a median for all samples of two. In Phase II, 47 different pharmaceuticals were detected in all source-water samples, with median concentrations in source water below 113 ng/L (Furlong et al., 2017). Therefore, chemical contaminants indicate the possibility of exposure to drinking water sources and the whole ecosystem. A substance suspended in the air must kill 50% of test animals during a predetermined observation period. Lethal Concentration (LC_{50}) values are frequently used as a general indicator of a substance's acute toxicity. The ThermoFisher safety data sheet (Scientific, 2012) reported that the ecotoxicity levels of metronidazole for freshwater fish at $LC_{50,}$ which is greater than 100 mg/L/96 h, are categorized as carcinogenic. Adopting the toxicity of 100 mg/L/96 h to be metronidazole toxicity in this study, Thus, from; equation.

$$Risk\,quotient=\frac{Measured\,concentration}{Reference\,concentration}=\frac{0.104}{100}=0.00104$$

$$\therefore RQ<1$$

We apply the same equation to other sampling points, metronidazole risk quotients in sampled sites, results are presented in Table 2.

Table 2: Represents metronidazole concentration at sampling points and calculated risk quotients (RQ)

Sample	Sampling Codes	Concentration	Risk Quotient	Implications
S1	IN 1	0.1044	0.001044	
S2	C11	0.0796	0.000796	

S3	C12	0.069	0.00069	RQ ¿1; A quotient of less than or equal to 1; suggests that negative consequences are unlikely to occur, so the risk is low.
S4	IN2	0.1008	0.001008	
S5	C21	0.0748	0.000748	
S6	C22	0.07	0.0007	
S7	C23	0.0876	0.000876	
S8	EF	0.0778	0.000778	
S9	TW	0.065	0.00065	
S10	DW	0	0	

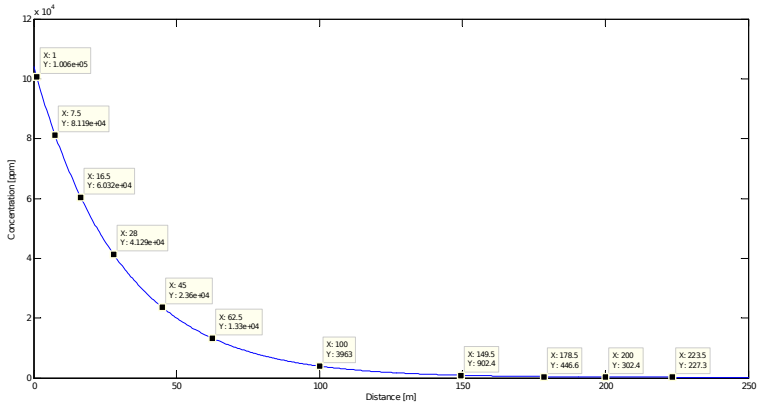
DW-Distilled Water; TW- Tape Water; EF- Effluents; IN 1- Iffluent; C11 to C23-Other sampling points;

Exposure refers to estimated environmental concentration (EEC), and toxicity refers to an adequate level or endpoint obtained from ecotoxicity testing, such as an LC_{50} or NOEC. Risk and hazard quotient is essential concepts used in risk assessment and used by a regulatory authority such as USEPA to explain the risk category of chemical substances (Finkel & Gray, 2021). A hazard quotient less than or equal to 1 indicates that adverse effects are not likely to occur, thus having negligible hazard. HQs greater than 1 are not statistical probabilities of harm to occur. Instead, they are simply stating whether and how much an exposure concentration exceeds the reference concentration (RfC) (Finkel & Gray, 2021).

Modeling output and its implications

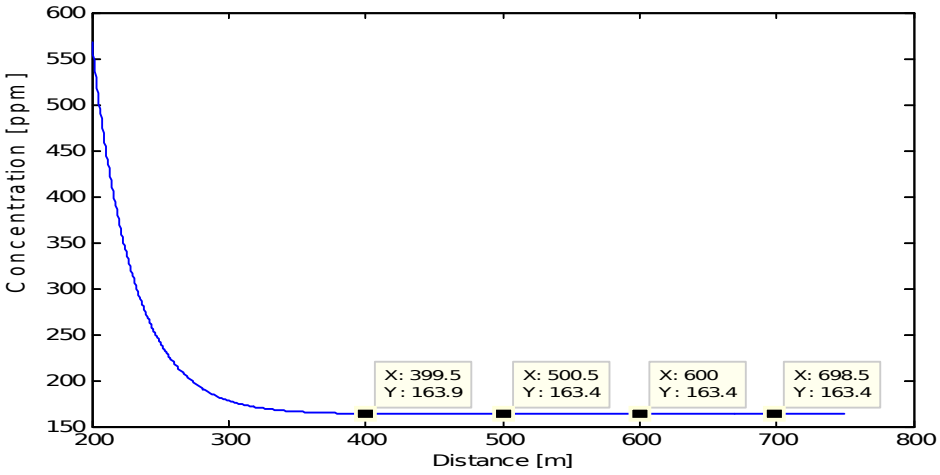
The conceptual framework on the application of ADE in modeling the transport of pharmaceuticals, particularly metronidazole, focused on understanding essential factors affecting the mobility of contaminants. The main element is the advection movement of water (Van Genuchten et al., 2013), which transports pollutants from the point source with moving water. In this case, either suspended, adsorbed, or dissolved form contaminants migrate with carrying water current (Van Genuchten et al., 2013). On the contrary, the dispersion factor remains a natural concentration-gradient-based process enhanced by water turbulence. Both factors seem to affect the mobility of a contaminant in the surface flowing waters similarly as reported by Martinus et al. (2013) (Van Genuchten et al., 2013). Computations of Equation 7 through Matlab software require necessary dependent and independent variables. Among dependent variables include the concentration of contaminants which was 0.104 ppm, velocity of water (u) of water, which was 0.041 m/s, as the, shear velocity (U^*), whose upper limit was calculated to be 0.589 m/s, dispersion coefficient (D_x) whose upper value was 0.0786 m^2/s, psylon (ε) whose upper value was 0.0514, μ obtained from upper limit was 0.00306, and alpha value (γ) whose range is between zero to one. Manning's constant (n) is the only independent variable, whose upper limit is 0.033. when these values are numerically solved by using Matlab software ith a command promt clear all; d=0.5; m=0.00306; K=104000; v=0.041; E=0.0514; D=0.0786; x=0:0.5:250; c=(d/m)+(K-(d/m))*exp(x*(v-E)/(4*D)); plot(x,c,'b'); xlabel('Distance [m]'); ylabel('Concentration [ppm]'); Z=[x' c']; they give Figure 1.

Figure 1**. 1-D numerical solution for advection-dispersion equation between 0 to 250 m**



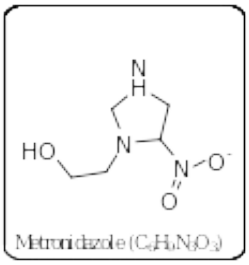
Contrary, the use of concentration at ppm values (K=0.104 ppm) instead of ppt results in the inverted Figure 2 which does not give a clear interpretation of the results. At a distance of 200 m from the point source, the concentration gradient is still predictable. Beyond 200 m whereby K=302400; and x=200:0.5:750; Figure 2 indicates the concentration gradient.

Figure 2**. Extended 1-D numerical solution for advection-dispersion equation between 200 to 750 m**



When using all values obtained from Manning's upper limit (n = 0.022), the model predicts that longitudinal transport of contaminants can be predicted up to a distance of 500 m, whereby there were insignificant concentration changes beyond it. These predictions conform with the theory that as pollutants move in the river, dilutions, absorption, evaporation, and extraction occur, leading to a gradual decrease of concentration downstream, as reported by other researchers (Pérez Guerrero et al., 2013). The obtained amount of metronidazole was predictable to a distance of 0 m to 200 m and 200 m to 750 m, as indicated in Figure 1 and Figure 2, respectively. A similar study reported by Miraji et al. conducted at the Msimbazi river showed that the model could predict contaminants concentration gradient up to 200 m, while the rise was insignificantly changing (Hossein et al., 2018). However, this holds on the understanding that there are no sink or secondary sources along the river (Whitehead et al., 2021). Factors such as too much dilution may necessitate sediments in the river to act as sink [93], affecting contaminant mobility predictability.

Scheme 4: Chemical Structure Of Metronidazole



Nevertheless, metronidazole is hydrophobic (Seedher et al., 1999); Scheme 4 represents its structure; it may undergo bio-accumulation in the fatty tissues of aquatic organisms. Furthermore, it may bio-magnify to high trophic levels through the food chain, resulting in bioconcentration, as reported by other researchers (Ali et al., 2018). Apart from other effects of metronidazole, bioconcentration in the living organisms may further exacerbate toxic effects; reports of its bioaccumulation in living tissue are available (Ali et al., 2018). For example, a study by Ali and Colleagues reported quantifiable levels of Pharmaceuticals and Personal Care Products (PPCPs) in marine biota from the Saudi Red Sea with a maximum metronidazole concentration of 82 ng/g DW in Silver Biddy fish (Ali et al., 2018). Pilla *et al.* (2020) evaluated the impact of metronidazole administration, alone or combined with a hydrolyzed protein diet, on the fecal microbiome and metabolome, BA metabolism, faecal lactate production, and in the serum metabolome of a population of healthy dogs. Results indicated the ability of metronidazole to change microbiome composition in G2 and G3, including decreases in richness ($P < .001$) and in crucial bacteria such as Fusobacteria ($q < 0.001$) that did not fully resolve four weeks after metronidazole discontinuation. In addition, the faecal dysbiosis index was significantly increased ($P < .001$). Those changes resulted in increased faecal total lactate ($P < .001$) and decreased secondary BAs deoxycholic acid and lithocholic acid ($P < .001$) (Pilla et al., 2020). Even at low concentrations, metronidazole as an emerging contaminant in a class of pharmaceuticals may induce physiological changes and, therefore, significantly risk the ecosystem.

Figure 3. Inverted concentration gradient curve

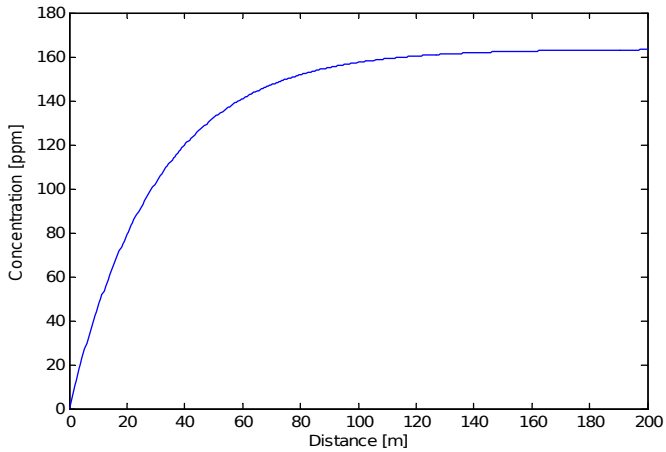


Figure 1 represents an uphill location between 0 m to 200 m, and the concentration range was 73,760 ppt. In comparison, the downhill location between 200 m to 750 m, concentration range was 13,900 ppt. The rate of change between 0 m to 50 m was tremendous with a gradient of;

$$Concentration\,gradient\left(\frac{ng}{L}\bullet\frac{1}{m}\right)$$

$$¿\frac{\Delta \in concentration}{\Delta \in distance}=\frac{1.04*10^5-1.33*10^4}{0-62}=-1463\frac{ng}{L}\bullet\frac{1}{m}$$

Emerging contaminants, particularly organic ones, have a high affinity with suspended settled organic and sediments, thus becoming primary consumers of suspended emerging contaminants. This phenomenon is never a permanent condition as during high dilutions like rain season, and the same media become sinks of ECs. The insignificant changes of concentration from 500 m are never a guarantee for safety. Yet, pharmaceuticals at trace levels may have induced micro-physiological changes that may affect tiny aquatic organisms over time. It may result in resistance genes against metronidazole treatment (Wang et al., 2015).

CONCLUSION

Quantified concentrations of metronidazole in this study may be seen as insignificant with an acceptable risk quotient. However, contrarily, even low concentrations of these chemicals may alter the microbiome of exposed aquatic organisms that may interfere with normal functioning. Hence, the toxic effect may be induced again in the long term, threatening ecological safety. Furthermore, the effects of contaminants such as pharmaceuticals are more than just toxicity. Instead, an alteration of the impact by additive effects from the combined concentration of chemicals acting by similar mode, increased concentration via bioaccumulation, bioconcentration and biomagnification through the food chain. Therefore, evaluating these substances and improving treatment schemes to remove or degrade contaminants is inevitable.

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